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Syphilis and HIV Infection

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Introduction:

The Immunology Clinic is a consultation practice for patients with HIV/AIDS and other immunological disorders located at The Toronto Hospital, Western Division. There are over 500 active HIV patients attending the clinic. Since June 1988 patients have been routinely screened for syphilis using both the VDRL and treponemal antibody tests. A chart review determined both the prevalence of positive syphilis serology and certain clinical observations--as well as any history of syphilis and treatment.

Previous reports indicate a high prevalence of latent syphilis in HIV/STD populations (ref 1-4). There are certainly questions emerging about the sensitivity of the clinical and serologic diagnosis of syphilis in the HIV/AIDS setting (ref 5-8). Newer techniques, using recombinant antigens and monoclonal antibodies are being evaluated alongside the standard approach, often resulting in intriguing findings.

Our goal was to expand our profile of the HIV positive patient with respect to a history of syphilis and/or a serologic finding of persistently reactive treponemal tests.

Method:

A patient's chart was included in the review if any of the following three inclusion criteria was met: 1.) a history of syphilis. 2.) a reactive treponemal test at any time. 3.) absolute CD4+ < 200/mm3.

We further collected data on age, gender, the most recent CD4+ count, the date of HIV diagnosis, and the date(s) when a reactive treponemal test was found.

We have established a treatment protocol for late latency. The treatment is 2.4 MU Benzathine Penicillin G weekly for three weeks plus Doxycycline 200 mg bid for 28 days. Many of our patients have been treated empirically and we are trying to discern any risk or benefit.

Results:

One hundred and two (102) patients' charts met the inclusion criteria. Fourteen (14) had missing data--either we had not asked for the history during initial consultation, or we had no serologic test results, due to less active charts. The results therefore reflect eighty-eight (88) patients.

The age range was 26-67 years with a mean of 42. There were 86 males and 2 females. The crude prevalence of treponemal antibody was 61% (54/88). The prevalence of treponemal antibody in whom a positive result would be expected was 90% (54/60), as 6 of our 34 patients with non-reactive treponemal tests had a definite history. For these 6 patients we found the CD4+ counts ranged 27-170, mean 78. These cases were not early syphilis.

None of the 88 patients has ever had clinical evidence of primary or secondary syphilis or neurosyphilis since coming to our clinic. There was no evidence of relapses based either on VDRL results or clinical signs/symptoms, despite 11 patients (20.4% of the reactive treponemal tests) who had reactive test results without a history. The mean CD4+ count for these 11 patients was 289.

We consider all the patients in whom there was either a history or a positive treponemal test result to have latent syphilis, and we recommend therapy. In addition, we offer the treatment empirically to those with severe immunosuppression. In the majority of cases, syphilis was diagnosed several years before the diagnosis of HIV. However, in two patients the diagnosis was coincident. Both patients continue to have persistent chronic treponemal reactions. To date, there seems to be no risk and little discernable benefit from the treatment protocol.

Discussion:

Our findings in this study provide consistent evidence that there is a high rate of late latent syphilis in certain subgroups of HIV patients, possibly associated with greater immunosuppression There are conflicting definitions of latent syphilis (ref 9,10).

The identification of a further six patients with very low CD4+ counts and a selective loss (ref 11,12) of their treponemal antibody sometime in the distant past is very significant. It is also important that 11 patients were identified as syphilitic with no history.

We are trying to address some of the classical questions such as definitions for latency and immunity in syphilis, as well as what is adequate therapy, and how to detect re-infected cases.

A debate between two schools of thought is emerging after 40 years of consensus. The first school believes that syphilis is only morbid in the presence of tissue destruction and the associated non-treponemal test reactivity. Recent American papers, where syphilis is treated in HIV infection, seem to belong to this school. The second school, toward which we lean, because we treat empirically, is the historical suggestion that there may be an indirect morbid effect of T. pallidum in the absence of normal screen test reactivity. There is an overwhelming association emerging in the literature between these two infections (ref 13-15) and interaction is of obvious concern.

Questions are now being raised about adequate treatment and how best to measure this treatment effect, especially in later syphilis cases (ref 16,17). It was once said that HIV infected persons with concomitant syphilis may need anti-syphilitic treatment for the rest of their lives(ref. 18). These persons, some serofast, some relapsers or failures, have undoubtedly existed by the thousands since the mid-1970's, and we are concerned as to why this did not become an issue in AIDS/STD care until the latter part of 1987. Furthermore, it did not become an issue for systematic therapeutic investigations until the 1990s. Where did the earlier cases of syphilis go with their innumerable sexual contacts? Only a small portion of the active cases were ever reported to public health for contact tracing (ref 19,20). Why was relapse not reported, again by the thousands, and why was the CNS involvement with T pallidum almost never reported in the first 8 years of the AIDS epidemic? This is despite the acknowledged existence of several hundred thousand untreated cases (ref 21) in the at-risk STD group and the known high rate of CNS sequestration of this parasite. If syphilis is not relapsing atypically in the HIV+ population, where are the cases in the non-HIV STD population? Most syphilis reported to public health authorities in the industrialized democracies throughout the seventies was occurring in gay males (ref 22,23). We therefore wonder whether lumbar punctures need be routinely a part of HIV care in the HIV/STD setting considering the question of drug levels in the CNS? Should syphilis be included in the differential diagnosis of all CNS pathology in HIV disease?

Syphilis is a chronic disease, and at the outset of the penicillin era, latency constituted seventy percent of the burden for the United States Public Health Service according to Stokes (ref24). The sub-optimal older treatments with metals, often in non-compliant cases, induced latency. Late syphilis was hard to treat, and many cases from the pre-penicillin era did not do well on penicillin(ref.25,26).

Several authors have suggested that biologic cure in syphilis is an open question (ref 28-30). If T. pallidum persists in some cases, especially those treated later, we would expect an effect on the clinical and serological sensitivity of diagnosis in the super-infected high risk person. Some authors claim "immunity" but we believe that this immunity is relative to all the collateral influences identified in syphilis infection (ref 31). The question raised by Chesney and Neisser (ref 32). and reiterated by Beerman (ref 33), as to whether immunity to syphilis is "concomitant" or "acquired" or a combination of both, remains unanswered.

Are we just now recognizing how re-infection would appear in the immune suppressed? Could HIV or SIV predispose to atypical infection with syphilis (ref.27)? And what would be the effect of a prior immunizing infection with syphilis on the sensitivity of the VDRL in re-exposure?

Prior to 1960, authors noted that the longer the original infection persisted before treatment, the lower the sensitivity of the VDRL/non-treponemal tests upon re-exposure (ref.34,35). Using the rabbit as an experimental model, it has been demonstrated that the sensitivity of the VDRL could approach zero in re-infection despite redissemination of treponemes to distal (popliteal) lymph nodes in all cases (ref.36,37). They further emphasized that the immunologic pattern in syphilis, once established by a few months of infection, could not be reversed by the arseno-bismuth treatment or subsequent penicillin (ref.38,39).

Ludwig Fleck stated in 1935 that a "thought collective" established the reliability of the Wassermann reaction as a scientific fact, despite an acknowledged sacrifice of sensitivity for the sake of specificity and reproducibility(ref.40). Collagen auto-antibodies, of

which the VDRL is one, have been reported in significant portions of AIDS patients (ref 41-43). Whatever specificity this finding has for syphilis, it is usually not being evaluated as such, sometimes because a treponemal test is non-reactive (ref.44). A historian of immunology has recently reiterated the lack of a satisfactory explanation for the auto-antibodies in syphilis (ref.46). Others have noted that antibody does not behave anamnestically in many cases of relapsing human syphilis (ref. 47). Joseph Earle Moore pointed this out in 1942 (ref.48). Careful clinical and serological follow-up are therefore both indispensable after the presumably curative therapy.

It seems to us that a subset of persons develop only an infection immunity to syphilis. This appears as lesion immunity, the significance of which remains unknown. The lesion immunity in no way precluded successful re-inoculation (ref.49) and so the question of excess mortality from silent infection persisted. Vaccines could usually assure lesion immunity but not sterile immunity, except in the case of Jim Miller's 37 week immunizing experiment in rabbits, or by the passage of immune lymphocytes in inbred animals (ref.50). A vaccine for syphilis looks very far off.

The question of silent infection so intrigued such authors as Paul Rosahn (ref.51), Trygve Gjestland (ref.52), and Joseph Earle Moore (ref.53), as well as the actuaries Hall and Dublin, that quite a controversy emerged by 1955 around the indirect, e.g. non-tissue destructive, mortality of syphilis. Gjestland could conceive of no mechanism for the susceptibility of syphilitics to pneumonias, TB, and cancers, so he was inclined to agree with Schamberg's position that syphilis was mortal only by the direct effect of its lesions (ref.54). Moore, in his consideration of many views, felt that syphilis was greatly underestimated as a killing disease. These authors did not have the tools such as affordable treponemal screening tests and CD4+/CD8+ phenotypes to examine the thousands of relapsing TB patients dying of consumption in sanatoria, or the hundreds of children reported in the 1950,s with autopsy findings of PCP and inclusion body disease, strongly suggesting disseminated CMV (ref.55,56).

In recent years, the indispensable role of the immune system for a successful therapeutic outcome in syphilis has been emphasized (ref.57). Further hypothesizing, we suggest that many syphilitics are de-sensitized to perhaps some T. pallidum antigens by untreated primary exposure and/or super-infections, at least as far as DTH reactions (ref.58) and the selective loss of treponemal antibody might suggest. It has been suggested that progression towards true immunologic tolerance to treponemal antigens occurs (ref 59). There was a larger school of thought in syphilology, before the HIV epidemic took over so much STD resources, that CMI in syphilis was (at least selectively) weakened (ref 60-62) and that early vigorous treatment was critical to restore the naive and vigorous immune response, should re-exposure occur. Undertreatment was considered far worse than no treatment.

We hypothesize (and invite comments) that an attempt be made to assess and re-sensitize the syphilis-anergic RES in the manner of the often miraculous results (ref 63,64) obtained by the use of tuberculin in old and anergic TB cases. We suggest that latent syphilis is controlled by the host, not the therapy. Treponemicidal drugs can only arrest a recrudescence, and thereby save the individual from both immediate peril and further immune depletion. We suspect that the late syphilis prevalent in these HIV/STD populations may be untreatable by current methods. However, we do what we can with our imperfect tools, antibody tests and cell-wall synthesis inhibition. A way is needed to assess and screen cell-mediated immune competence to T. pallidum, if the interaction of syphilis and HIV is ever going to be clarified.

Recent long-term observations of HIV-infected haemophiliacs (ref 65,66) and parenteral drug users (ref 67,68) suggest there are controllable co-factors, which profoundly effect the AIDS incidence in these groups. A comparable benefit for the gay male cohorts, which are the focus of most AIDS research and funding in the US, has yet to be found. Sadly, AZT has again become controversial. It may be that an immunologic therapy for syphilis which would boost CMI against T. pallidum will be required before the currently available drugs are effective.

Summary/Conclusion:

We discovered a high rate of reactive treponemal tests in our study population. We are probably the first group to look at the correlation of serologic evidence of "true" latent syphilis infection (i.e. nonreactive VDRL) to the degree of HIV related immunosuppression as measured by the surrogate marker CD4+ T-lymphocyte count. Concern is emerging that HIV, with its associated immunosuppression, necessitates higher doses of antibiotic treatment, or different choices of antibiotic treatment, both at primary and secondary stages as well as for latent syphilis (ref 69,70). We may be missing symptoms or signs of neurosyphilis in our clinic population because this has not been a specific focus, or because it may have an atypical presentation (ref 71,72).

We determined a 61% crude prevalence rate of reactive treponemal tests in those analyzed, and an overall rate in the entire group of 11% (54/500). And yet we did not find any reactive VDRL tests in 500 STD clinic patients! Does this latter finding mean that HIV patients could become (re)infected with syphilis, without any serological evidence? The patients with chronically reactive treponemal tests had moderate immune suppression with a mean CD4+ count of 272. We estimate that the mean CD4+ count in our clinic population is about 400.

It is noteworthy that there was one subgroup of 6 patients with a history of syphilis and non-reactive treponemal tests, as well as evidence of severe immunosuppression with a mean CD4+ count of 78. This finding suggests that some patients lose their immune response to the Treponeme because of severe HIV-related immunosuppression. It would be extremely useful to retrospectively analyze this cohort.

Our review demonstrates that is important to determine the history and the probability of syphilis in all patients presenting with and being followed for HIV/AIDS care. In two patients the diagnosis of

syphilis coincided with that of HIV. It is also important to screen serologically with treponemal tests as well as the VDRL. Significantly, 11 patients had reactive treponemal tests but no history of syphilis. Their CD4+ counts averaged 289, corresponding to the total group with chronically reactive treponemal tests. These 11 patients would have been missed had the treponemal tests not been done. Our protocol as mentioned above is used to treat all patients with chronically reactive treponemal tests regardless of the VDRL titre,and is offered to all patients with CD4+ < 200. We have not yet been able to discern a benefit, but the risk seems very low.

Table 1

		Treponemal Test		
		+	-	
History of Syphilis	**Yes**	**43**	**6**	**49**
	No	**11**	**28**	**39**
		54	**34**	**88**

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